sequester AR-NOX comprising incubating AR-NOX with a test agent and detecting, if present, an AR-NOX-test agent complex.

At the outset, Applicants respectfully point out that the presently claimed invention recites a method that requires the identification of agents that bind AR-NOX from a collection of test agents with unknown binding activity. Thus, the presently claimed invention is not directed to discovering every possible chemical compound that binds to AR-NOX. Applicants submit that there is no requirement that the specification guarantees the success of the claimed method in identifying every possible chemical compounds.

An enabling description for a process or method requires sufficient disclosure as to "how to carry out the claimed process." In re Barrett, 440 F.2d 1391, 1392 (C.C.P.A. 1971). For example, in Barrett, the court held that a claimed process for producing thoria sol by electrodialysis using "an anion permeable membrane" was sufficiently enabled without restriction as to the type of anion permeable membrane to be used. 440 F.2d at 1393. The court found that although "the proper selection of the membrane *is* critical because certain anion permeable membranes might not be operative in the process, there is nothing in the record to suggest that, even if this is so, the selection of an appropriate membrane would not have been within the ordinary skill in this art at the time appellants' parent application was filed." 440 F.2d at 1392. "If selection of an appropriate membrane would have been within the ordinary skill in the art at that time, appellants' disclosure is just as sufficient as if the selection criteria were set forth at length in the specification." 440 F.2d at 1393 (citation omitted) (emphasis added).

In the present case, Applicants respectfully submit that ordinary skill in the fields of biochemistry and drug screening technology is high and the specification is enabling for an artisan of ordinary skill to perform the screening assays of the presently claimed invention. The specification has provided methods for isolating and characterizing AR-NOX and thus, based on such teachings, AR-NOX can readily be used in screening assays well known to one of skill in the art. A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). The specification need only be reasonable with respect to the art involved; they need not

inform the layman nor disclose what the skilled already possess. General Electric Co. v. Brenner, 159 USPQ 335, 337 (D.C. Cir. 1968).

Furthermore, Applicants submit that based on the teachings in the specification and the skill in the art of drug screening, only routine experimentation is required to practice the invention with agents that are not explicitly disclosed in the specification. With respect to the Examiner's contention that an incredible amount of experimentation would be required to discover every possible chemical compound that binds to AR-NOX, Applicants respectfully submits that any such experimentation would merely be routine. According to applicable case law, an invention is enabled even though the disclosure may require some routine experimentation to practice the invention. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). Considerable amount of experimentation is permitted if it is merely routine or the specification provides reasonable amount of guidance and direction to the experimentation. In re Jackson, 217 U.S.P.Q. 804, 807 (1982).

The Examiner contends that the specification recites the use of antibodies as test substances but is silent regarding other possible test substances. First, Applicants respectfully disagree and points out that according to applicable case law, under 35 U.S.C. § 112, an inventor is not required to disclose "a test of every species encompassed by their claims" even in an unpredictable art. In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976) (emphasis in original). Moreover, there is no requirement that an application have any working examples, even when the invention involves a complex technology. See In re Strahilevitz, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982).

Specific examples of other possible test substances described in the specification as originally filed include ubiquinone or ubiquinone derivatives which are used as a base molecule of a combinatorial chemistry library (see, *e.g.*, page 16, lines 13 to 20), proteins (see, *e.g.*, page 16, line 31 to page 17, line 10), and antisense and ribozyme molecules (see, *e.g.*, page 17, lines 11 to 28).

Next, Applicants respectfully direct the Examiner to Section 5.5 (page 15, line 9 to page 17, line 36) of the specification as originally filed. In this section, Applicants describe *in vitro* and *in vivo* methods for screening for agents which target AR-NOX. *In vitro* selection methods include methods which measure a binding interaction between two or more components and methods which measure the activity of an enzyme which is one of the

interacting components, *i.e.*, AR-NOX. As described in the specification on page 15, line 16 to page 12, binding interactions between two or more components can be measured in a variety of ways known in the art. Methods which measure the activity of AR-NOX are described in Section 5.4 (page 14, line 1 to page 15, line 7). Thus, Applicants respectfully submit that the specification as filed is enabled for one of skill in the art to screen for agents that sequester AR-NOX comprising incubating AR-NOX with a test agent and detecting an AR-NOX-test agent complex.

The Examiner points out that the working examples of the instant specification are directed toward screening methods wherein antibodies are the test substances. Applicants point out that under the applicable case law, it is improper to limit Applicants to the specific example presented, notwithstanding the disclosure and enablement of a broader invention. *See* In re Anderson, 176 U.S.P.Q. 331, 333 (C.C.P.A. 1973); In re Kamal, 158 U.S.P.Q. 320, 323 (C.C.P.A. 1968).

Applicants respectfully submit that the claimed subject matter is described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant invention is fully enabled for test agents because (a) the claimed invention is directed to a method of screening for agents that bind AR-NOX, not a method for identifying every chemical compound that binds to AR-NOX, (b) screening assays are well known to one of skill in the art, (c) various screening assays are set forth in the specification, and (d) putative test agents, in addition to antibodies, are described in the specification. Where a disclosure provides considerable direction and guidance on how to practice the invention and presents working examples, and where, at the time of application, the skill in the art was quite high and the methods needed to practice the invention well known, a conclusion of enablement should be made. In re Wands, 858 F.2d 731, 740, 8 U.S.P.Q.2d. 1400, 1406 (Fed. Cir. 1988).

Accordingly, Applicants respectfully submit that the Examiner's rejection under 35 U.S.C. § 112, first paragraph, has been overcome and respectfully request that the rejection be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 103(a), SHOULD BE WITHDRAWN

The Examiner has rejected claims 12 to 16 and 20 to 23 under 35 U.S.C. §

103(a) as being unpatentable over Morré et al. (U.S. Patent No. 5,605,810, hereinafter "Morré") in view of Wheelock et al. (U.S. Patent No. 6,140,063, hereinafter "Wheelock") in further view of Asard et al. (Plas. Mem. Redox. Systems, hereinafter "Asard"). The Examiner has also rejected claim 24 under 35 U.S.C. § 103(a) as being unpatentable over Morré in view of Wheelock in further view of Asard. Applicants respectfully disagree.

The objective standard for obviousness under 35 U.S.C. § 103 as set forth clearly by the Supreme Court of the United States in Graham v. John Deere Co., 383 U.S. 1 (1966) requires the Examiner to ascertain: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; and (3) the differences between the claimed subject matter and the prior art. *See* 383 U.S. at 17. The obviousness or nonobviousness of the claimed subject matter must be determined in light of these inquiries. Moreover, the Graham Court also explained that secondary considerations such as commercial success, long felt but unsolved needs, failure of others, *etc.* might be utilized in determining the obviousness or nonobviousness of the invention.

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. A finding of obviousness requires that the prior art suggest to those of ordinary skill in the art (1) that they should carry out the invention and (2) that they would have a reasonable expectation of success in so doing. The question to be addressed is whether the combination of the above-cited references teaches all the elements and limitations of the present invention. Specifically, the combination of references cited above must teach every element of the subject invention.

In particular, the Examiner alleges that Morré teaches NADH oxidase as a target for a variety of uses in diagnosis and therapy but lacks exemplification of a method of screening and disclosure of ubiquinone; Wheelock teaches that testing compounds that inhibit biochemical functions for treating diseases is known in the art; and Asard teaches plasma membrane redox systems and their role in biological stress and disease. The Examiner contends that it would have been obvious to one of ordinary skill in the art to combine the above teachings and obtain a method of screening agents that sequester NADH oxidase. Applicants respectfully disagree.

Morré describes a NADH oxidase ("NOX") which is specific to neoplastic or cancer cells. The isoform of NOX that is specific to cancer cells and is immunologically and

biologically different from NOX associated with normal cells, is known as tNOX (see, *e.g.*, page 8, line 18 and page 9, lines 30 to 36 of the specification). In fact, the invention of Morré is directed to the use of tNOX as a marker to identify neoplastic cells, (see, *e.g.*, abstract of Morré). The tNOX described in Morré differs from the AR-NOX of the presently claimed invention.

The presently claimed invention is directed to another distinct isoform of NOX, namely AR-NOX, which is specific to sera from elderly patients (see, *e.g.*, page 8, line 17 and page 13, lines 6 to 10). As reviewed in Asard on page 122 to 123 in Section 1.3. titled "NADH Oxidase Activity Forms", there are characteristics that distinguish NADH oxidase isoforms, such as different functional characteristics and responses to activators and inhibitors. For example, tNOX is hormone-insensitive and responsive to anti-tumor drugs (see, *e.g.*, page 9, lines 30 to 36 of the specification and Table 1 of page 123 of Asard).

AR-NOX differs from other isoforms of NOX in that (a) reduction of cytochrome c occurs spontaneously (see, *e.g.*, page 28, lines 10 to 14), (b) AR-NOX has superoxide generating activity (see, *e.g.*, Table 3, page 27, lines 1 to 14), (c) AR-NOX has an augmented oscillation period (see, *e.g.*, page 28, lines 24 to 27 and Figure 2B), and (d) AR-NOX is resistant to inhibition by retinoic acid (see, *e.g.*, page 28, lines 27 to 30). The characteristics that distinguish AR-NOX from the other isoforms are elaborated below.

Reduction of cytochrome c (as a measure of superoxide formation) occurs spontaneously in AR-NOX. As shown in Table 4 and lines 10 to 14 of page 28 of the specification, reduction of cytochrome c by the seras of aged patients occurred spontaneously. In contrast, reduction of cytochrome c in carcinoma and epithelial, *i.e.*, non-cancer, cells was induced by UV (see, *e.g.*, Table 3 of page 27 of the specification). Unlike the UV-induced changes with cells, the reduction of cytochrome c by sera of aged patients occurred spontaneously (*i.e.*, no need for UV induction) (see, *e.g.*, lines 10 to 12 of page 28 of the specification). Furthermore, the reduction of cytochrome c by AR-NOX in the sera of aged patients was partially inhibited by SOD and inhibited by coenzyme Q (see, *e.g.*, page 28, lines 12 to 14). Thus, one difference between AR-NOX and the other isoforms of NOX is the spontaneous reduction of cytochrome c.

Another difference between AR-NOX and the other isoforms of NOX is the augmented oscillation period. As described on page 28, lines 15 to 24 of the specification, NOX activities of cells, plasma, sera, and the purified protein oscillate with a period of 24

minutes (also reviewed in Asard on page 131 to 133 in Section 3.4. titled "Periodicity"). In contrast to the other NOX isoforms, AR-NOX has an augmented oscillation period of 26 minutes.

A further difference between AR-NOX and the other NOX isoforms is that AR-NOX is resistant to inhibition by retinoic acid, *i.e.*, AR-NOX is not inhibited by retinoic acid (see, *e.g.*, page 28, lines 27 to 30). In contrast, an isoform of tNOX, tNOX β, is resistant to retinoic acid (see, *e.g.*, Table 1 on page 123 of Asard).

Morré does not teach or suggest the use of AR-NOX as a target. As discussed above, Morré is directed toward using NOX associated with neoplastic cells, *i.e.*, tNOX, as a target for assays and screening drugs which are specific for neoplastic cells. Furthermore, Morré does not teach or suggest any disease states (*e.g.*, oxidative stress or age-related disorders) which are characteristic of the disease states in which AR-NOX is expressed on the cell surface or shed into sera. The NOX described in Morré as a target, *i.e.*, tNOX, differs from the target NOX of the present invention, *i.e.*, AR-NOX. Thus, Morré cannot make obvious the presently claimed invention because Morré does not teach or suggest the AR-NOX isoform let alone its use as a target to identify agents for treatment of disease states such as oxidative stress or age-related disorders.

Wheelock does not correct the deficiency of Morré by describing that testing compounds that inhibit biochemical functions for treating diseases is known in the art. Wheelock does not teach or suggest NOX, let alone AR-NOX.

Asard describes four NOX isoforms: CNOX, tNOX α, tNOX β, and dNOX (see, *e.g.*, page 123, Table 1). Asard does not teach or suggest the AR-NOX isoform. Asard speculates that NOX has a potential role in oxidative stress and aging (see, *e.g.*, page 147, Section 6.2), however, Asard postulates that the potential role of NOX in oxidative stress and aging is as a terminal oxidase of a plasma membrane electron transport chain. Asard hypothesizes that when electron transport to molecular oxygen or protein disulfides is disrupted, superoxide or other reactive oxygen species could be generated at the expense of cytosolic NAD(P)H + H^+. Asard does not teach or suggest a NOX isoform that has spontaneous superoxide generating activity, an augmented oscillation period, or resistance to retinoic acid like the AR-NOX isoform described in the specification as originally filed (see, *e.g.*, Table 3, page 27, lines 1 to 14 and page 28, lines 10 to 14 of the specification). Thus, Asard does not correct the deficiency of Morré.

Thus, the combination of Morré, Wheelock, and Asard does not teach or suggest the presently claimed invention, *i.e.*, a method for screening for agents to sequester AR-NOX, because none of the references teach or suggest the AR-NOX isoform, which as described in the specification as originally filed, is specific to sera from elderly patients.

With respect to the rejection of claim 24, the Examiner alleges that it would have been obvious to one of ordinary skill in the art to combine the teachings of Asard with that of the combined references and obtain a method of screening wherein the presence of disulfide-thiol interchange in the substrate is detected. Applicants respectfully disagree and reiterate the above arguments, *i.e.*, that the combination of Morré, Wheelock, and Asard does not teach or suggest the presently claimed invention, *i.e.*, a method for screening for agents to sequester AR-NOX, because none of the references teach or suggest the AR-NOX isoform.

The Examiner has rejected claims 17 to 19 under 35 U.S.C. § 103(a) as being unpatentable over Morré in view of Wheelock in further view of Garrett et al. (Biochemistry, hereinafter "Garrett"). The Examiner contends that Garrett discloses the biochemical workings of the electron transport chain. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to combine the teachings of the combined references with those of Garrett and obtain a method of screening for agents that inhibit NADH oxidase by incubating a mixture comprising NADH oxidase, a test agent, cytochrome c, and a substrate capable of generating oxygen species.

The Examiner has rejected claims 17 to 19 under 35 U.S.C. § 103(a) as being unpatentable over Morré in view of Wheelock in further view of Garrett. Applicants respectfully disagree. As discussed above, the combination of Morré, Wheelock, and Asard does not teach or suggest the AR-NOX isoform.

Garrett describes the biochemical workings of the electron transport chain. Contrary to the Examiner's assertion, Garrett does not teach or suggest NOX, let alone AR-NOX. Instead, Garrett describes the oxidation of NADH by coupling it to with the reduction of a-ketoglutarate to isocitrate (see, *e.g.*, page 633, lines 7 to 9 of Garrett) and the flavoprotein NADH-Coenzyme Q reductase (see, *e.g.*, page 635, lines 22 to 29 of Garrett), both of which are distinct from NOX. Since Garrett does not teach or suggest NOX, let alone the AR-NOX isoform, Garrett does not correct the deficiency of Morré, Wheelock, or Asard. Since the combination of Morré, Wheelock, Asard, and Garrett do not teach or suggest the

AR-NOX isoform, the combination cannot teach or suggest the presently claimed method of screening for agents that sequester AR-NOX.

Applicants also respectfully point out that the Examiner has used Applicants' own specification to conclude that it would be obvious to modify the teachings of Morré, Wheelock, Asard, and Garrett to generate the screening method of the presently claimed invention by relying on the legally impermissible use of hindsight to hold the teachings of the applicant against itself. "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983). Only after reviewing the Applicants' specification can the Examiner arrive at the combination of cited references to reconstruct the claimed invention; however, as described above, the cited references neither alone nor in combination, teach or suggest the method of Applicants' claimed invention.

Accordingly, Applicants respectfully submit the Examiner's rejections under 35 U.S.C. § 103(a) has been overcome and respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks into the file history of the above-identified application. Applicants believe that each ground for rejection or objection has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the application are respectfully requested.

Respectfully submitted,

By: Laura A. Coruzzi 40,258

Date December 4, 2002

Laura A. Coruzzi 30,742

Laura A. Coruzzi (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosures